Remarks

Reconsideration of this Application is respectfully requested.

Claims 1 and 4-12 are sought to be amended, and new claims 13 and 14 are sought to be added. Support for the amendment to claim 1 can be found, for example, in the specification at page 8, line 1 to page 10, line 16, and at page 13, line 12 to page 14, line 19. Claims 4-11 were amended merely to bring the claims into conformance with amended claim 1. Support for the amendment to claim 12 can be found, for example, in the specification at page 6, lines 28-29. Support for new claims 13 and 14 can be found, for example, in the specification at page 14, lines 11-19. Upon entry of the foregoing amendment, claims 1-14 are pending in the application, with claim 1 being the independent claim.

The specification was amended to correct obvious typographical errors. Applicants submit that one skilled in the art would not only recognize the existence of the error in the spelling of "ISCOVE'S DNEM," but the correction as well, *i.e.* DMEM (Dulbecco's modified Eagle's medium). In addition, support for the amendment to the amount of ethanolamine in Table 1 can be found in Tables 2 and 3.

The above changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Priority

The Examiner acknowledged Applicants' claim for foreign priority based on Argentine Application Nos. 98 01 05611, filed November 6, 1998, and 99 01 00681, filed February 23, 1999, but noted that certified copies of the applications had not been filed as required by 35 U.S.C. § 119(b). (*See* Office Action, page 2, ¶ 1.) In accordance with 35 U.S.C. § 119(b)(3) and 37 C.F.R. § 1.55(a)(2), Applicants will submit certified copies of the foreign priority applications before a patent issues from the present application.

Rejections under 35 U.S.C. § 102

The Examiner rejected claims 1-3 and 6 under 35 U.S.C. § 102(b) as allegedly being anticipated by Jixian *et al.*, *Bull. Acad. Mil. Med. Sci. 21*:244-246 (1997) (hereinafter "Jixian"). (*See* Office Action, page 2, ¶ 2.) In particular, it is the Examiner position that

> Jixian et al[.] teaches production of recombinant human erythropoietin (rHuEPO) using CHO cells in a serum free media (SFM-p) in the presence of insulin. Regarding claims 1-3 specifically the cited art teaches genetically engineered mammalian cells (CHO cells), which express recombinant human erythropoietin. Regarding claim 6 the cited art teaches culturing of rHuEPO producing cells in a fetal calf serum-free media designated as SFM-p. The cited art further teaches that the SFM-p comprises various additives, which include Se, Ethanolamine, vitamins, peptone, insulin, transferin [sic] and some cytokines added in DMEM and F12 medium. In addition the cited art teaches that SFM-p promotes growth and proliferation of rHuEPO expressing CHO cells, which resulted in the production of rHuEPO in culture media. Thus the cited art clearly anticipate the invention as claimed.

(Office Action, page 3, ¶ 2.) (citations omitted.) Applicants traverse this rejection as it may apply to the present claims.

Anticipation of a claim under § 102 can be found only if the prior art reference discloses each and every element as set forth in the claim. *See Glaxo Inc. v. Novopharm Ltd.*, 34 U.S.P.Q.2d 1565, 1567 (Fed. Cir. 1995), *cert denied,* 116 S. Ct. 516 (1995). Further, "[a]n anticipating reference must describe the . . . [claimed] subject matter with sufficient clarity and detail to establish that the subject matter existed and that its existence was recognized by persons of ordinary skill in the field of the invention." *ATD Corp. v. Lydall Inc.*, 48 U.S.P.Q.2d 1321, 1328 (Fed. Cir. 1998). Therefore, in order for the Jixian reference to anticipate the claimed invention, it must describe each and every limitation of Applicants' claimed invention such that the subject matter would be recognized by one skilled in the art.

The claimed invention is directed to a method for obtaining human erythropoietin comprising culturing mammalian cells which express recombinant human erythropoietin in cell expansion culture medium and then culturing the mammalian cells in culture medium comprising insulin, where the cell expansion medium and the insulin-containing medium contain less than 2 grams per liter of glucose. However, the process described in the Jixian reference requires the addition of large amounts of glucose, in the order of tens of grams per liter of culture medium per day. *See* Jixian translation at page 6 ("A large amount of glucose is required in cell growth and metabolism so that higher glucose consumption indicates higher cell density.").

Since Jixian does not teach using culture medium containing insulin which contains less than 2 grams per liter of glucose and since anticipation requires that each and every element of a claim be found within a single prior art reference, it is clear that

the present invention is not anticipated by the Jixian reference. Therefore, Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) be withdrawn.

Rejections under 35 U.S.C. § 103

The Examiner rejected claims 4 and 5 under 35 U.S.C. § 103(a) as allegedly being obvious over Jixian in view of Koch *et al.*, EP Application No. 0 513 738 A2 (hereinafter "Koch"). (*See* Office Action, page 3, ¶ 3.) Specifically, it is the Examiner position that

> It would have been obvious to one of ordinary skill in the art at the time of filing to modify the teaching of Jixian by incorporating the SFM-p with insulin in the range of 1-20mg/L in view of Koch. One would have been motivated to do so because incorporation of insulin in the range of 1-20mg/L in serum free media is close to cultivation conditions when serum is used. One would have a reasonable expectation of success to produce rHuEPO in CHO using serum free media containing insulin in the range of 1-20mg/L because the cited prior [art] clearly teaches that CHO cells proliferate and produce recombinant EPO under such conditions.

(Office Action, page 5, ¶ 2.) (citation omitted.) Applicants traverse this rejection as it may apply to the present claims.

In order to establish a *prima facie* case of obviousness, the Examiner must satisfy three basic criteria. First, there must be some suggestion or motivation, either in the references cited by the Examiner or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or combine reference teachings to obtain Applicants' invention. *See In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998). Second, there must be a reasonable expectation of success. *See In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991.) Third, all

the claim limitations must be taught or suggested by the prior art references. *See In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). The suggestion to make the claimed combination, as well as the reasonable expectation of success, must be found in the prior art references, not in Applicants' disclosure. *See In re Vaeck*, 947 F.2d at 491, 20 USPQ2d at 1442 (Fed. Cir. 1991.)

Applicants assert that there is no suggestion or motivation in Jixian or Koch to combine the teachings to obtain Applicants' invention. Moreover, even assuming, *arguendo*, that such a suggestion or motivation to combine the references is present, there would be no expectation of success in generating the claimed invention and all of the claim limitations are not taught or suggested by the references.

As pointed out by Applicants above, Jixian fails to teach a method for obtaining human erythropoietin comprising culturing mammalian cells which express recombinant human erythropoietin in cell expansion culture medium and then culturing the mammalian cells in culture medium comprising insulin, wherein both the cell expansion medium the medium containing insulin contain less than 2 grams per liter of glucose. In further contrast to the present invention, Jixian teaches that it is necessary to continuously check the glucose concentration that is present in the medium in order to provide the growing cells with a suitable environment. *See id.* This additional step results in further complications which are not present in the claimed process. Koch fails to remedy the deficiencies of Jixian.

Koch discloses a serum-free culture medium that in addition to insulin, contains monosaccharides from 0.3 to 10 g/L. *See* Koch translation at page 3. Koch also teaches that during the cultivation of the cells, 40-200 g/L of glucose is added to the culture medium. *See id.* The additional glucose is added because "the growth can be maintained

at a relatively high rate over a long period of time and higher cell quantities can be produced than when the culture medium is used directly and the corresponding compounds are consumed right from the start." Koch translation, page 4. Accordingly, Koch does not teach using low amounts of glucose in the cell expansion cell medium. Rather, in contrast to the claimed invention, Koch teaches that large amounts of glucose are required in the cell expansion cell medium in order to maintain high cell growth.

Obviousness cannot be established by modifying the teachings of the prior art to produce the claimed invention unless there is some teaching, suggestion or motivation to do so found either in the reference itself or in the knowledge generally available to one of ordinary skill in the art. *See In re Fine*, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988). Based on the disclosures of Jixian and Koch, there is no teaching, suggestion or motivation to use culture medium which contains less than 2 grams per liter of glucose. In addition, the mere fact that the Jixian or Koch references could conceivably be modified to make the claimed invention does not render the resultant modification obvious unless the prior art also suggests the desirability of that specific modification. *See In re Mills*, 16 U.S.P.Q.2d 1430 (Fed. Cir. 1990). The prior art references clearly fail to do so.

In addition, Koch teaches that, besides insulin, there are other substances that can affect the growth of mammalian cells, such as transferrin. *See* Koch translation at page 2, paragraphs 1 and 2. In order to avoid the use of animal proteins which can be contaminated with pathogenic viruses, Koch employs a water soluble iron compound instead of transferrin. A critical aspect of the Koch disclosure is, besides the addition recombinant insulin from prokaryotes, the addition of a water-soluble iron compound as a transferrin substitute. *See* Koch translation at page 2 and claim 1. That is, Koch employs a substitute of transferrin as an extra source of the iron which is normally

provided by the mixture which is used to prepare the culture medium. It is clear, then, that Koch teaches that besides insulin, a substitute of transferrin is crucial in order for the growing cells to proliferate adequately. Contrary to the Koch disclosure, a water-soluble iron compound to substitute for transferrin in the culture medium is not required in the present invention.

As such, not only does Koch fail to teach all of the limitations of the claimed invention, but in fact teaches a person of ordinary skill in the art to *not* expect to achieve a reasonable expectation of success in producing recombinant EPO without a substitute of transferrin as an extra source of iron. Accordingly, it is respectfully requested that the this rejection under 35 U.S.C. § 103(a) be withdrawn.

The Examiner rejected claims 7-10 under 35 U.S.C. § 103(a) as allegedly being obvious over Jixian in view of Yanagi *et al.*, *DNA 8*:419-427 (1989) (hereinafter "Yanagi") and Chiba *et al.*, U.S. Patent No. 3,865,801 (hereinafter "Chiba"). (*See* Office Action, page 5, ¶ 4.) It is the Examiner's position that

> it would have been obvious to one of ordinary skill in the art at the time of filing to modify the invention of Jixian by employing purification strategy to concentrate EPO containing media as taught by Yanagi. One would have been motivated to do so because highly purified preparation of EPO is desirable product for clinical uses. In addition it would have been further obvious to store the purified EPO preparation in a frozen state in view of Chiba, since cyropreserved [sic] proteins have increases [sic] stability. One would have a reasonable expectation of success in doing so, since purification of recombinant proteins from the host cells and cyropreservation [sic] of purified protein was routing in the art at the time of filing.

(Office Action, page 6, ¶ 4.) (citations omitted.) Applicants traverse this rejection as it may apply to the present claims.

In order to establish a *prima facie* case of obviousness, the Examiner must demonstrate, *inter alia*, that all the claim limitations are taught or suggested by the prior art references. *See, e.g. In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). As discussed above, Jixian does not teach or suggest the presently claimed invention. With respect to Yanagi and Chiba, the Examiner asserted that

> Yanagi et al[.] teach[] isolation of recombinant human erythropoietin produced by Namalwa cells. Regarding claim 7(c) and 9-10 the cited art teaches separation of EPO containing supernatant from EPO-producing 2A311 cells. The cited art further teaches concentration of EPO form [sic] the cell supernatant. . . . Chiba et al[.] teach[] a method of storing EPO for prolonged periods of time. Regarding claim 7 (d), the cited art teaches storing purified EPO preparation in the frozen state at -20°C.

(Office Action, page 6, ¶ 4.) (citations omitted.)

Applicants submit that neither Yanagi nor Chiba remedy the deficiencies of Jixian, in that they, alone or in combination, fail to teach a method for obtaining human erythropoietin comprising culturing mammalian cells which express recombinant human erythropoietin in cell expansion culture medium and then culturing the mammalian cells in culture medium comprising insulin, wherein both the cell expansion medium the medium containing insulin contain less than 2 grams per liter of glucose. Therefore, Applicants submit that the Examiner has failed it establish a *prima facie* case of obviousness with respect to claims 7-10 and respectfully request that this rejection be withdrawn.

Finally, the Examiner rejected claims 7, 11 and 12 under 35 U.S.C. § 103(a) as allegedly being obvious over Jixian, Yanagi and Chiba and further in view of van Reis, U.S. Patent No. 5,490,937 (hereinafter "van Reis"). (*See* Office Action, page 7, ¶ 5.) The Examiner concluded that

> it would have been obvious to one [of] ordinary skill in the art at the time of filing to modify the invention of Jixian, Yanagi and Chiba by employing a purification strategy that involves a tangential filtration system and sterile filtration in view of van Reis. One would have been motivated to use tangential filtration system to accomplish large-scale resolution macromolecular mixtures obtained form [sic] cell culture media. One would have a reasonable expectation of success, since isolation of protein via tangential flow filtration process was routine in the protein purification art at the time of filing.

(Office Action, page 8, ¶ 5.) (citations omitted.) Applicants traverse this rejection as it may apply to the present claims.

As discussed above, the cited art references must teach or suggest all of the claim limitations in order to establish a *prima facie* case of obviousness. Applicants have demonstrated that neither Jixian, Yanagi nor Chiba teach or suggest the presently claimed invention. Regarding the van Reis reference, the Examiner asserted that

> Van Reis et al[.] teaches a tangential flow filtration process and apparatus for separating species of interest (proteins) from a mixture. Regarding claim 11 the cited art teaches a tangential filtration system through filtration membranes having a pore size that separate species of interest having molecular weight of about 1 to 1000kDa. . . . Regarding claim 12, the cited art further teaches filtration through micro porous membranes that has a pore size typically from 0.1 to 10 micrometers, which would inherently sterile the filtered product.

(Office Action, page 8, ¶ 5.) (citations omitted.)

Van Reis is directed to processes for separating compounds of interest from a mixture which comprises subjecting the mixture to tangential flow filtration where the filtration membrane has a specific pore size. Similar to the other cited references, Applicants submit that van Reis does not remedy the deficiencies of Jixian, in that it does not, alone or in combination with Yanagi or Chiba, teach a method for obtaining human

erythropoietin comprising culturing mammalian cells which express recombinant human erythropoietin in cell expansion culture medium and then culturing the mammalian cells in culture medium comprising insulin, wherein both the cell expansion medium the medium containing insulin contain less than 2 grams per liter of glucose. Accordingly, Applicants submit that the Examiner has failed it establish a *prima facie* case of obviousness of claims 7, 11 and 12 and respectfully request that this rejection be withdrawn.

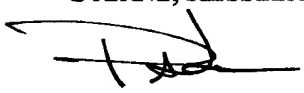
Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



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